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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,995	10/05/2001	John P. McKearn	CU-2560 RJS	4037

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Richard J Streit
Ladas & Parry
Suite 1200
224 South Michigan Avenue
Chicago, IL 60604

EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	14

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/857,995	John P. McKearn et al
Examiner	**Art Unit**
Sudhaker Patel	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 11, 2002

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-106 is/are pending in the applica

4a) Of the above, claim(s) 4-10, 12-20, 22-27, 47-53, 55-70, and 103-106 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3, 11, 21, 28-46, 54, and 71-102 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 13 dated 6/11/02 is acknowledged.

(1). Restriction/election:

Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse(MPEP 818.03(a)).

Applicants have elected invention of **Group I,** claim(s)(in part) 1-3,11,21,28-46,54,71-102, drawn to simple compositions, a method use, and method of making composition wherein MMP inhibitors are of Group F). having core as: ***6-membered Heterocycle with 2 heteroatoms of which one atom is N-SO2-C nonheterocyle*** i.e. Compound # 11 of claim 29 having **thiomorpholine** molecule in the structure, classified in class **544**, subclass 58.2, class 514 subclass 227.8, and Irinotecan or Topotecan together with radiation for treatment of neoplasia. Claims 4-10,12-20,22-27,47-53,55,56,57-70,103-106 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Accordingly, this application with be examined bearing in mind the subject matter of invention of Group I and the species as elected by the applicants. Accordingly, applicants are urged to correct the claims and their dependency in reply to this Office Action.

(2). ***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3,11,21,28-46,54,71-102 are rejected under 35 U.S.C. 112, para one because the specification, while enabling as a method of treating neoplasm related to lung, does not reasonably provide enablement for treating or preventing other neoplasia disorders encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to " method of treating or preventing neoplasia disorder in a Mammal and the specification provides that these disorders include Germ cell cancer, Prostate cancer, Breast cancer, Ovarian cancer, Gastrointestinal cancers " etc.

The specification discloses the method and combination using two or more components with at least on component being matrix metalloproteinase inhibitor, and the additional component or components is optionally selected from :

(A). Anti-angiogenesis agent;

(B). Antineoplastic agent;

(C). Adjuvant agent;

(D). Immunotherapeutic agent;

(E). Device;

(F). Vaccine;

(G). Analgesic agent;

(H). Radiotherapeutic agent

with the proviso that cycloxygenase-2 inhibitor is excluded(see page 9 lines 13-30)..

The Biological assay method(s) provided on pages 216-222 disclose:

(I). The compounds M14 with cisplatin for Pancreatic Cell (PC-3 Model);

and **not** Compound 11/ AG 3340 demonstrated the ability to affect response;

(II). The compounds M14 with taxol for Breast Tumor Model and **not** Compound 11/AG 3340 demonstrated to affect response;

(III).The compounds M14 with cyclophosphamide for MX-1 Adjuvant Model and **not** Compound 11/AG 3340 for tumor regression;

(IV).The compounds M14 with taxol for MX-1 Breast Tumor with taxol and **not** Compound 11/AG 3340 demonstrated to affect response;

(V). The compounds M14 with taxol for SK-mes Tumor with taxol and **not** Compound 11/AG 3340 demonstrated to affect response;

(VI).The compounds M14 with Irinotecan for HT-29 and **not** Compound 11/AG 3340 demonstrated to affect response.

Claims 1-3,11,21,28-46,54,71-102 read on any and all disorders related to degradation of the extracellular matrix including those yet to be discovered for which there's no enabling disclosure.

There is no demonstration for the ability to treat disorders as claimed herein by "a process of administering to a mammal in need thereof a therapeutically-effective amount of a combination of a matrix metalloprotease inhibitor and one or more antineoplastic agents.

Combination therapy using MMP inhibitors and antineoplastic agents as recited in the claims reads on all such moieties regardless of complexity of structure and point of attachment to the heterocyclic core for which there is insufficient teaching regarding how to use the claimed method with all the possible combination of compounds encompassed by their generic activity as inhibitor and agent. There is undue burden involved for one skilled in the art in using the combinations of compounds instantly claimed in the instant treatment or prevention. Applicants provide no reasonable assurance that any and all combinations of compounds as outlined above, will have ability to generate the compounds either in vivo &/or in vitro by one or more processes/method(s). Applicants have not provided any data pertinent to "in vivo" tests, and also no nexus has been provided to show how the in vitro data correlates to it for the elected invention of Group I.

We know little of the pharmacology and toxicology of these combinations of compounds". See Heath et al (PubMed Abstract : 10852638, and Drugs 2000 May, 59/5,1043-55) wherein the authors state that " Several MMPI compounds and their combination with chemotherapy have entered phase II therapy trails, but it is still too early to report any data".

Belotti et al(PubMed Abstract: 10669951; Int. J. Biol Markers 1999 Oct-Dec; 14/4;232-8) also report that expected mechanism of action of treatment with MMPI alone or in combination

with cytotoxic therapy and the difference in side effects compared to cytotoxic drugs make the definition of end points and assessment of response difficult. Furthermore, it is not yet clear whether tumor vascularization or, more specifically, MMP expression/activation should be a criterion of eligibility for this kind of treatment.

It is also noted by Liekens et al(PubMed Abstract: 11172729, and Biochem Pharmacol 2001 Feb 1, 61/3,253-70) that " Synthetic inhibitors of cell invasion(AG-3340) or compounds that interfere with angiogenic growth factors or their receptors, as well as endogenous inhibitors of angiogenesis are being evaluated in clinical trials against a variety of solid tumors. As basic knowledge about the control of angiogenesis and its role in tumor growth and metastasis increase, it may be possible in the future to develop specific anti-angiogenic agents that offer a potential therapy for cancer and angiogenic diseases".

Hidalgo et al(PubMed Abstracts: 11158186, and J Natl Cancer Inst 2001 Feb 7, 93/3,178-93) also states that " the development of the MMPI, like that of other targeted and predominantly antiproliferative compounds, poses a challenge because the paradigm that have governed the design of clinical oncology trials may not be relevant to this new class of agents".

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:

(1). The nature of invention;

(2). the state of prior art ;

(3). the predictability or lack thereof in the art;

(4). the amount of direction or guidance present;

(5). the presence or absence of working examples;

(6). the breadth of the claims, and

(7). the quantity of experimentation needed.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the for the treatment of disorders by the combination of compounds as claimed herein. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, " the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24(CCPA 1970).

Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits. The facts provided as above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorder as recited herein.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use as a method of treatment as claimed herein.

In view of the breadth of the claims, the nature of the invention, the unpredictability of ligand-receptor interactions in general, and lack of working examples regarding the activity of

the compositions and their combinational therapy, one having ordinary skill in the art would have to undergo an undue experimentation to use the invention commensurate in scope with the claims.

(3). ***Specification***

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

This application has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is, therefore, requested in promptly correcting any errors of which they may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

S.p.July 7, 2002.